RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE

IN THE U.S. PATENT AND TRADEMARK OFFICE

August 3, 2005

Applicants: Futoshi OKADA et al

For: ANTI-TUMOR AGENT

Serial No.: 10/655 567 Group: 1651

Confirmation No.: 6434

Filed: September 4, 2003 Examiner: Kosson

Atty. Docket No.: Furuya 1407

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

LETTER TRANSMITTING APPEAL BRIEF FEE

Sir:

Enclosed is Appellants' check in the sum of $1,520 representing payment of the Appeal Brief fee ($500) and a three month time extension ($1,020). The Commissioner is hereby authorized to charge any additional fee which may be required by this paper, or to credit any overpayment, to Deposit Account No. 06-1382. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

IN DUPLICATE

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Encl: Appellants' Brief on Appeal
Claims Appendix
Evidence Appendix
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APPELLANTS' BRIEF ON APPEAL

Sir:

This is an appeal from the decision of the Examiner in the Advisory Action dated May 13, 2005, finally rejecting Claims 16-23.

REAL PARTY IN INTEREST

Asama Chemical Co., Ltd. and Combi Corporation are the assignees of the present application and the real parties in interest.

RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences to present application Serial No. 10/655 567.

STATUS OF CLAIMS

Claims 16-23 are pending in the present application and are the claims on appeal. Claims 1-15 have been canceled.

STATUS OF AMENDMENTS

The Amendment After Final Rejection dated April 19, 2005 has been entered into the prosecution record of the present application.

SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention, as defined by independent Claim 16, is directed to a method of inhibiting the malignant progression of a tumor in a subject comprising the step of administering to the subject in which the malignant progression is to be inhibited a pharmacologically effective amount of a superoxide dismutase combined with gliadin (specification page 5, lines 5-14).

Claim 17 limits Claim 16 in requiring that the superoxide dismutase is a melon superoxide dismutase (specification page 5, lines 5-10).

Claim 18 limits Claim 16 in requiring that the superoxide dismutase combined with gliadin is a melon superoxide dismutase coated with gliadin (specification page 5, lines 3 and 4).

Claim 19 limits Claim 16 in requiring that the superoxide dismutase combined with gliadin is administered orally or parenterally (specification page 4, last 2 lines).

Appellants' invention, as defined by independent Claim 20, is directed to a method of inhibiting the metastasis of a tumor in a subject which comprises the steps of administering to the subject in which the metastasis is to be inhibited a pharmacologically effective amount of a superoxide dismutase combined with gliadin (specification page 8, lines 1-24).

Claim 21 limits Claim 20 in requiring that the superoxide dismutase be a melon superoxide dismutase (specification page 4, lines 27-29).

Claim 22 limits Claim 20 in requiring that the superoxide dismutase combined with gliadin be melon superoxide dismutase coated with gliadin (specification page 4, lines 28 and 29).

Claim 23 limits Claim 20 in requiring that the superoxide dismutase combined with gliadin is administered orally or parenterally (specification page 4, last 2 lines).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The ground of rejection to be reviewed on appeal is whether Claims 16-23 are unpatentable under 35 USC 103(a) over Murcia et al in view of Postaire et al and Ginoux.

ARGUMENT

The presently claimed invention is directed to a method for inhibiting the malignant progression and the metastasis of a tumor in a subject which comprises the steps of administering to the subject in which the malignant progression and metastasis are to be inhibited a pharmacologically effective amount of a superoxide dismutase combined with gliadin.

As discussed in the present specification, prior to the present invention, it was known that superoxide dismutase, hereinafter referred to as SOD, was an antioxidant enzyme that catalyzed the conversion of a super-oxide to hydrogen peroxide and was known as an enzyme which played an essential role in protecting the body from oxidative damages. It was known to orally or parenterally administer a preparation of SOD molecules coated with lipids or protein to effect local treatment of certain cancers and illnesses of the digestive system. That is, conventional SOD preparations did not effect SOD levels at any tissues and only acted by itself as an antioxidant at the site of the drug administration and so the SOD-containing compositions were orally administered in order for the SOD to contact directly with tumors located in the digestive tract before inactivation of the SOD occurred by proteinases contained in the digestive juices.

It had previously been thought that SOD inhibited the anti-cancer activity of treatment regimens using x-ray radiation, anti-cancer drugs and anti-tumor activity of immune

leukocytes because the reactive oxygen generated by x-ray radiation, various anti-cancer drugs and macrophages in NK cells killed cancer cells through the release of reactive oxygen. In fact, a reference of record, British Journal of Cancer, 2000 October: 83(7): 928-934, reports that an increase of SOD in cancer cells diminishes the cytotoxic effect of several anti-cancer modalities and inhibition of SOD activity augmented anti-cancer activity of radiation and some anti-cancer drugs.

The instant invention is based on the discovery that the SOD composition of the present invention functions as an induction agent for post-antioxidant enzymes, including SOD, catalase and glutathione peroxidase, and therefore is essentially different from conventional SOD preparations which do not effect the SOD levels at any tissues and only acts by itself as an antioxidant at the site of the drug administration. As such, the treated SOD of the present invention can inhibit tumor growth and malignant progression, including metastasis, at sites other than where the drug is administered. It is respectfully submitted that the prior art cited by the Examiner does not disclose the presently claimed invention.

The Murcia et al reference discloses that several Mediterranean and tropical fruits have antioxidant activity and evaluates the antioxidant or scavenger activity of different fruits, including melon pulp homogenate, by estimating activities against the hydroxyl radical, HOCl and hydrogen peroxide. This reference has no disclosure with respect to the SOD activity of the Mediterranean and tropical fruits because SOD activity is measured only when dismutation activity of O_{2^-} is present in melons since all plants and animals have SOD activity as an essential body constituent. As explained previously, conventionally administered SOD only works locally and does not work throughout the body and, as such, there is no disclosure in this reference which would suggest to one of ordinary skill in the art that SOD combined

with gliadin could be used to treat tumors at any site in the body other than the administration site.

Ginoux et al discloses that a soluble *Cucumis melo* protein extract has a superoxide dismutase enzyme activity. This reference discloses that this protein extract is useful for cosmetic purposes, medical purposes, such as anti-cancer agents for the digestive system and as an antioxidant, and food purposes, such as the replacement of synthetic antioxidants. Although Ginoux et al does disclose that the protein extract having an elevated superoxide dismutase activity can be used to treat certain cancers of the digestive system, as discussed previously, this is only due to the fact that orally administered SOD contacts directly with tumors located in the digestive tract before inactivation of the SOD occurs by proteinases contained in the digestive juices. As such, there is no suggestion in this reference that SOD treated with gliadin would have any unexpected properties as compared with untreated SOD.

Postaire et al discloses pharmaceutical compositions that are suitable for the oral administration of superoxide dismutases and used in the treatment of inflammatory processes, such as rheumatism and fibrosis, viral processes, such as HIV infection, and toxic conditions associated with the presence of substantial amounts of oxygen, such as central nervous system disorders, ischemia, non-vascular gastrointestinal disorders, eye disorders or control of the undesirable effects of anti-cancer treatments. Although this reference discloses that the superoxide dismutase could be administered with prolamines, such as gliadin, this reference has no disclosure which suggests that the treated SOD shown there could be used in the treatment of cancerous tumors.

OBJECTIVE TEST DATA IS OF RECORD IN THE PRESENT APPLICATION WHICH IS SUFFICIENT TO REBUT ANY SHOWING OF PRIMA FACIE OBVIOUSNESS OF CLAIMS 16-23 UNDER 35 USC 103(a)

Enclosed in the Evidence Appendix attached hereto is a Declaration Under 37 CFR 1.132 executed on April 13, 2005, which compares the anti-tumor agent of the present invention with gliadin and SOD for the prevention of tumor formation and metastatic ability of tumor cells. In the appended Declaration, the procedures of the Example on pages 6-10 of the present application were followed to generate test data that illustrated the efficacy of the present invention in inhibiting the malignant progression of a tumor. Mice were co-implanted with QR-32 cells and a gelatin sponge in order to induce the formation of tumors in the mice. Oral preparations containing SOD-G according to the present invention, physiological saline solution and gliadin were administered to the mice. The results are shown in Table 2 in the enclosed Declaration under "Experiment A". As seen by the results of Experiment A in Table 2 of the appended Declaration, the mice that were administered the SOD-G of the present invention had a significantly lower occurrence of tumors (41%) than the mice that were administered the physiological saline solution (79%) and the gliadin (83%).

Additionally, as shown under "Experiment B", the lung-colonizing ability of the cell line arising from the mice which were treated with SOD-G had a much lower incidence of metastasis. In Table 3, the inhibition of the long metastatic ability of the tumor cell lines arising from the mice having the co-implanted QR-32 cells and a gelatin sponge and treated with physiological saline solution, gliadin and SOD-G of the present invention is shown. Table 3 shows that the tumor cell lines arising in the mice that were administered the SOD-G of the present invention had a greatly reduced metastatic ability (97% reduction) than the tumor cells arising from the mice that were administered gliadin (17% reduction) or physiological saline solution (0% reduction).

In Table 4 of the Declaration Under 37 CFR 1.132, the procedures of Example 1 in the present specification were again followed in that mice were co-implanted with QR-32 cells and a gelatin sponge. The mice were then treated with physiological saline solution, purified melon SOD and the SOD-G of the present invention. As shown in Experiment A in Table 4, the SOD-G of the present invention had a much lower occurrence of tumors (44%) than the mice that were administered physiological saline solution (88%) or purified melon SOD (100%). Moreover, with respect to metastatic ability of the QR-32 cells, as shown in Column 5 of Table 4 in the Declaration Under 37 CFR 1.132, all six cell lines established from tumor nodules removed from SOD-treated mice, QRsP/SOD-1 to QRsP/SOD-6 were metastatic. On the other hand, none of the four cell lines recovered from the tumor nodules of the SOD-G treated mice had metastatic properties ($p < 0.01$). This illustrates that the SOD-G of the present invention unexpectedly inhibited malignant progression and metastatic ability while SOD, according to the prior art, did not.

The only reference cited by the Examiner which discloses a pharmaceutical composition comprising SOD and gliadin discloses the use of this composition in the treatment of inflammatory processes, such as rheumatism and fibrosis, viral processes and toxic conditions associated with the presence of substantial amounts of oxygen. There is no suggestion in this reference of utilizing SOD-G to inhibit the malignant progression of a tumor or metastasis.

The Murcia et al reference merely discloses that several Mediterranean and tropical fruits have antioxidant activity. There is no disclosure in this reference which would suggest to one of ordinary skill in the art that SOD, let alone SOD-G, could be used in the treatment of cancer tumors.

The Ginoux et al reference discloses the use of SOD from *Cucumis melo* extract for cosmetic purposes, anti-cancer agents for the digestive system and antioxidant, and food purposes

such as replacement of synthetic antioxidants. As admitted by Appellants previously, although this reference discloses that SOD could be used as an anti-cancer agent for the digestive system, this activity is only due to the direct contact with the SOD and the cancer cells and the digestive tract. As shown in the enclosed Declaration Under 37 CFR 1.132, the SOD-G of the present invention has unexpectedly superior properties over SOD, such as disclosed in Ginoux et al, with respect to the inhibition of formation of tumors and metastasis. The activity of SOD-G in the present invention is clearly unexpected in light of the prior art and establishes the patentability of the presently claimed invention thereover.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that the presently claimed invention is clearly patentably distinguishable over the prior art cited by the Examiner. Reversal of the Examiner is respectfully solicited.

Respectfully submitted,

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Encl: Claims Appendix
Evidence Appendix

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CLAIMS APPENDIX

16. A method of inhibiting the malignant progression of a tumor in a subject comprising the step of administering to the subject in which the malignant progression is to be inhibited a pharmacologically effective amount of a superoxide dismutase combined with gliadin.

17. The method of Claim 16, wherein the superoxide dismutase is a melon superoxide dismutase.

18. The method of Claim 16, wherein the superoxide dismutase combined with gliadin is a melon superoxide dismutase coated with gliadin.

19. The method of Claim 16, wherein the superoxide dismutase combined with gliadin is administered orally or parenterally.

20. A method of inhibiting the metastasis of a tumor in a subject comprising the step of administering to the subject in which the metastasis is to be inhibited a pharmacologically effective amount of a superoxide dismutase combined with gliadin.

21. The method of Claim 20, wherein the superoxide dismutase is a melon superoxide dismutase.

22. The method of Claim 20, wherein the superoxide dismutase combined with gliadin is melon superoxide dismutase coated with gliadin.

23. The method of Claim 20, wherein the superoxide dismutase combined with gliadin is administered orally or parenterally.

EVIDENCE APPENDIX

Declaration Under 37 CFR 1.132 dated April 13, 2005

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicants: Futoshi OKADA et al
For: ANTI-TUMOR AGENT
Serial No.: 10/655 567 Group: 1651
Confirmation No.: 6434
Filed: September 4, 2003 Examiner: Kosson
Atty. Docket No.: Furuya Case 1407

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

I, Hiroshi SHIONOYA, hereby declare as follows:

I am one of the co-inventors of the invention described and claimed in application Serial No. 10/655 567, filed on September 4, 2003.

I hereby incorporate by reference herein the contents of the Example contained on pages 6-10 of the above-identified application.

I have carried out additional tests to illustrate the unexpected properties of the anti-tumor agent of the present invention in inhibiting the malignant progression of a tumor.

The procedures of the Example contained on pages 6-10 of application Serial No. 10/655 567 to generate additional test data showing the efficacy of the present invention in inhibiting the malignant progression of a tumor. Additional mice were co-implanted with QR-32 cells and a gelatin sponge. The mice were then treated with a physiological saline solution, gliadin and SOD-G of the present invention. The results are shown in Table 2 below.

Table 2 Inhibition of inflammation-promoted acquisition of metastatic ability of QR-32 cells by SOD-G

[a] Experiment A: A: Tumorigenicity of QR-32 cells co-implanted with gelatin sponge in mice					[c] Experiment B: Characteristics of the arising tumor lines				
						Lung-colonizing ability		Other metastasis sites	
Treated with	No. of mice with tumor take/no. of mice treated(%) Exp. 1	Exp. 2	Total	[b] No. of cell lines established/ no of tumors tested(%)	Cell lines established From the arising tumor	Incidence (No. of mice with lung metastasis/no. of mice tested)	No. of lung with metastastic nodules	Incidence (No. of mice with other metastasis/ no of mice tested .	Sites (incidence)
-	-	-	-	-	QR-32	0/10	0,0,0,0,0,0,0,0,0,0	0/10	None
Saline	8/8 (89%)	7/10 (70%)	15/19 (79%)	15/19 (79%)	QRsP/-1	3/3 **d	1,3,14	0/3 NS	None
					QRsP/-2	3/3 **	8,13,20	0/3 NS	None
					QRsP/-3	4/4 **	3,8,14,>150	1/4 NS	[O (1/4)]
					QRsP/-4	3/4 **	0,1,3,35	0/4 NS	None
					QRsP/-5	4/5 **	0,2,8,15	1/5 NS	[O (1/5)]
					QRsP/-6	4/4 **	8,43,>150,>150	2/4 NS	[O (2/4)]
					QRsP/-7	4/4 **	8,11>150,>150	2/4 NS	[O (2/4)]
					QRsP/-8	4/4 **	>150,>150,>150,>150	0/4 NS	None
					QRsP/-9	4/4 **	16,48,51,62	0/4 NS	None
					Total	33/35 (94%)		6/35 (17%)	
Gliadin	8/8 (100%)	7/10 (70%)	15/18 (83%)	15/18 (83%)	QRsP/GD-1	4/4 **	2,2,4,17	0/4 NS	None
					QRsP/GD-2	4/4 **	5,8,12,14	0/4 NS	None
					QRsP/GD-3	2/4 NS	0,0,3,8	0/4 NS	None
					QRsP/GD-4	3/4 *	0,5,7,22	1/4 NS	[O (1/4)]
					QRsP/GD-5	3/4 *	0,3,6,12	0/4 NS	None
					QRsP/GD-6	4/4 **	2,5,6,7	1/4 NS	[O(1/4)]
					QRsP/GD-7	3/3 **	16,>150,>150	1/3 NS	[O (1/3),A(1/3)]
					QRsP/GD-8	4/4 **	25,58,132,>150	3/4 *	[O (2/4),LN(1/4)]
					QRsP/GD-9	4/4 **	58,73,>150,>150	0/4 NS	None
					QRsP/GD-10	4/4 **	42,43,123,>150	0/4 NS	None
					Total	35/39 (90%)		5/39 (13%)	
SOD-G	4/7 (57%)	6/10 (60%)	10/17 (59%)	7/17 (41%) p<0.05 vs saline	QRsP/OK-1	0/4 NS	0,0,0,0	0/4 NS	None
					QRsP/OK-2	3/4 *	0,2,3,18	0/4 NS	None
					QRsP/OK-3	2/4 NS	0,0,5,7	0/4 NS	None
					QRsP/OK-4	0/4 NS	0,0,0,0	0/4 NS	None
					QRsP/OK-5	1/4 NS	0,0,0,8	0/4 NS	None
					QRsP/OK-6	0/4 NS	0,0,0,0	0/4 NS	None
					QRsP/OK-7	1/4 NS	0,0,0,8	0/4 NS	None
					Total	7/28 (28%) p<0.01 vs saline		0/28 (0%) p<0.05 vs saline	

Table Legends

a: In Experiment A, 1 x 10^6 QR-32 tumor cells were co-implanted with gelatin sponge in mice to which oxykine, gliadin and saline as a control had been orally administered once daily from 2 days before tumor implantation and following 4 weeks. Doses of Oxykine and SOD were 10mg/kg (=10 U/kg as SOD activity) and equivalent amount of gliadin (0.2mg/kg). respectively in 0.2ml saline

b: Culture cell lines are separately established from tumors which had arisen in each mouse.

c: In Experiment B, 1 x 10^6 cell of each cell lines were intravenously injected into mice. Twenty-five days later, the mice were sacrified and the metastatic nodules on the lung surface were counted macroscopically.

d: $p<0.01$ vs incidence of QR-32 (0/10)

e: $p<0.05$ vs incidence of QR-32 (0/10)

f: not significant vs incidence of QR-32 (0/10)

g: O: ovary, A: asoites, LN: Lymph node

Tumor cell lines arising from the mice having the co-implanted QR-32 cells and a gelatin sponge and treated with the physiological saline solution, gliadin and SOD-G of the present invention were tested for lung metastatic ability. The results are shown in Table 3.

Table 3 Inhibition of lung metastatic ability of QRsP/OK tumor lines

Cell lines	Metastatic incidence (%)	Lung weight (g)	No. of lung metastatic nodules	Median value	Range	Percent reduction
QRsP	33/35 (94)	0.45±0.46	50.1±61.5	12	0-150	0
QRsP/GD	35/39 (90) a	0.37±0.39 b	41.5±55.9 a	15	0-150	17
QRsP/OK	7/28 (25) a	0.18±0.02 b	1.6±3.9 a	0	0-18	97

QRsP/OK tumor lines, shown in Table 2, are cell lines established from the arising tumor after subcutaneous transplantation of benign tumor cell of QP-32 with gelatin sponge into mice treated with SOD-G.
Cell lines QRsP and QRsP/GD are those which established from mice treated saline and gliadin, respectively.

a:$p<0.001$, b:$p<0.005$ as compared to QRsP/GD, Glyadin treated group of mice.

In Table 4 shown below, additional mice were co-implanted with QR-32 cells and a gelatin sponge. The mice were then treated with a physiological saline solution, SOD and SOD-G of the present invention. The SOD was purified melon SOD per se. The dose of SOD was 10 U/kg which was equivalent to 10 mg/kg of SOD-G. The results are shown below in Table 4.

Table 4 Inhibition of inflammation-promoted acquisition of metastatic ability of QR-32 cells by SOD-G

A: Tumorigenicity of QR-32 cells co-implanted with gelatin sponge in mice			Characteristics of the arising tumor lines				
				Lung-colonizing ability		Other metastasis sites	
Treated with	No. of mice with tumor take/no. of mice treated(%) Exp. 3	No. of cell lines established/no of tumors tested(%)	Cell lines established From the arising tumor	Incidence (No. of mice with lung metastasis/no. of mice tested)	No. of lung with metastatic nodules	Incidence (No. of mice with other metastasis/no of mice tested .	Sites (Incidence)
-	: : :	-	QR-32	0/10	0,0,0,0,0,0,0,0,0,0	0/10	None
Saline	7/8 (88%)	6/7 (86%)	QRsP/-10	3/3 ** a	3,8,150	0/3	None
			QRsP/-11	3/3 **	8,13,20	0/3	None
			QRsP/-12	3/3 **	10,14,>150	1/3	[O* (1/3)]
			QRsP/-13	2/3 * b	0,3,35	0/3	None
			QRsP/-14	3/3 **	2,8,15	1/3	[O (1/3)]
			QRsP/-15	1/3 NS c	0,0,3	1/3	[O (1/3)]
			Total	15/18		3/18	
SOD	7/7 (100%)	6/7 (86%)	QRsP/SOD-1	3/3 **	31,38,>150	1/3	[O,(1/3)]
			QRsP/SOD-2	2/3 *	0,5,38	0/3	None
			QRsP/SOD-3	3/3 **	10,41,58	0/3	None
			QRsP/SOD-4	2/3 *	0,9,18	0/3	None
			QRsP/SOD-5	3/3 **	6,6,30	0/3	None
			QRsP/SOD-6	3/3 **	36,62,>150	1/3	[O(1/4)]
			Total	16/18		2/18	
SOD-G	4/9 (44%) p<0.05 vs SOD	4/9 (44%)	QRsP/OK-8	0/3 NS	0,0,0	0/3	None
			QRsP/OK-9	1/3 NS	0,0,3	0/3	None
			QRsP/OK-10	1/3 NS	0,0,7	0/3	None
			QRsP/OK-11	0/3 NS	0,0,0	0/3	None
			Total	2/12 p<0.01 vs SOD p<0.01 VS saline		0/12	

*: Ovary
a; p<0.01 vs incidence of QR-32 (0/10)
b; p<0.05 vs incidence of QR-32 (0/10)
c; not significant vs incidence of QR-32 (0/10)

DISCUSSION OF RESULTS

As can be seen by the data contained in Table 2, the mice that were administered the SOD-G of the present invention had a significantly lower occurrence, 41%, of tumors than the mice that were administered the physiological saline solution, 79%, or the gliadin, 83%.

Additionally, the tumor cells arising in the mice that were administered the SOD-G of the present invention had a greatly reduced metastatic ability, 97% reduction, than the tumor cells arising from the mice that were administered gliadin, 17% reduction, or the physiological saline solution, 0% reduction.

As illustrated in column 2 of Table 4, the mice that were administered the SOD-G according to the present invention had a much lower occurrence of tumors (44%) than the mice that were administered the physiological saline solution (88%) or the purified melon SOD (100%).

With respect to the metastatic ability of the QR-32 cells, as shown in column 5 of Table 4, all 6 cell lines established from tumor nodules removed from SOD-treated mice, QRsP/SOD-1 to QRsP/SOD-6, were metastatic. In contrast thereto, none of the 4 cell lines recovered from the tumor nodules of the SOD-G treated mice were metastatic ($p<0.01$). This establishes that SOD-G inhibited malignant progression and metastatic ability while SOD did not.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: Apr. 13, 2005

Hiroshi Shionoya

Hiroshi SHIONOYA